7. (Amended) The method as recited in Claim 5 further comprising mixing the BMP-2 protein producing MSCs with a polymer either before, during or after topically applying the protein producing MSCs.

8. (Amended) The method as recited in Claim 5 wherein the protein producing MSCs are topically applied in a concentration of about 50 x 10^6 per ml of a pharmaceutically acceptable polymer and produce an effective amount of the protein.

REMARKS

Applicants thank the Examiner for the thoughtful response and kind suggestions of claim language in the Office Action of September 9, 2002.

Applicants note the Office's request for corrected drawings and state that the corrected drawings were submitted with the "Petition to Accept Color Photographs" filed on October 10, 2001.

Claims 1-8 are currently pending. Claims 1, 4-5, and 7-9 have been amended to point out more particularly and claim more distinctly the subject matter of the present invention. The Office has maintained the restriction requirement as set forth in the Office Action of September 9, 2002. In the Office Action of November 6, 2002, the Office set forth the following new rejections:

1) claims 5-8 were rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement;

2) claims 1-8 were rejected under 35 U.S.C. § 112, second paragraph, as indefinte;

3) claims 1 and 2 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Moutsatsos et al. (WO 99/11664);

4) claims 1, 2 and 4-7 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Riew et al. (Calcif. Tissue Int. 63:357-360 1998);

5) claims 1, 2 and 4-7 were rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Cheng et al. (Calcif. Tissue Int. 68:87-94, 2001);

6) claims 1 and 3-8 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Moutsatsos et al. in view of Riew et al. or Cheng et al.;

7) claims 1, 3, 5 and 8 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Riew et al. or Cheng et al.

These rejections are respectfully traversed for the reasons set forth below. Reconsideration is respectfully requested.

Applicants submit that no new matter has been added by way of this amendment.

I. Rejections under 35 U.S.C. § 112, second paragraph

The Office rejected claims 1-8 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. This rejection is respectfully traversed for the reasons set forth below.

Claim 1 (and dependent claims 2-4) has been amended to point out more particularly and claim more distinctly the subject matter of the claimed invention, and now reads "a plurality of bone marrow stromal cells (MSCs) comprising a vector comprising a DNA sequence encoding BMP-2 operably linked to a promoter." Claims 5-8 have also been amended and now set forth the relationship between the steps of a) to c) and the preamble as required.

In view of the above, Applicants respectfully submit that the rejected claims are definite. Accordingly, Applicants request the withdrawal of these rejections.

II. Rejections under 35 U.S.C. § 112, first paragraph

The Office rejected claims 5-8 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. This rejection is respectfully traversed for the reasons set forth below.

The Office argues that, while the specification enables a method of enhancing new bone formation in a subject, the specification does not enable the methods of treating defects or injuries to bone, cartilage, muscle, adipose or other fibrous tissues because the specification does not provide guidance to a skilled artisan on how to repair a defect in cartilage, muscle or adipose. The Office asserts that "there is no evidence of record indicating or suggesting that the expression of BMP-2 in MSCs could induce the transfected bone marrow stromal cells to differentiate into cells with phenotypes other than osteoblasts *in vitro* or *in vivo*..." (Office Action, at page 5). Applicants respectfully disagree.

Claims 5-8, as amended, are directed to a method of enhancing new bone, cartilage or connective tissue formation in a subject, comprising obtaining a plurality of bone marrow stromal cells (MSCs) from a subject, transducing the MSCs of step a) with a vector comprising a DNA sequence encoding BMP-2 operably linked to a promoter to generate BMP-2 protein producing MSCs, and topically applying the BMP-2 protein producing MSCs at a site requiring new bone, cartilage, or connective tissue formation on the subject, such that new bone, cartilage or connective tissue formation is enhanced. The Office acknowledges Applicants' enablement of a method of enhancing new bone formation in a subject. Applicants respectfully submit that it

was known in the art at the time of Applicants' invention that the expression of BMP-2 in pluripotent stem cells (such as bone marrow stromal cells) can induce the cells to differentiate into cell types other than osteoblasts, e.g., cartilage and connective tissue. See, e.g., Moutsatsos et al. (WO 99/11664), at, for example, page 8, lines 16-22, and page 9, lines 5-12. Thus, Applicants respectfully submit that the state of the art at the time of Applicants' invention combined with Applicants' disclosure properly enabled one ordinarily skilled to make and/or use Applicants' methods to enhance the formation of cartilage or connective tissue, as well as bone.

The Office also states that claims 5-8 encompass the implantation of autologous BMP-2 producing MSCs at any site on the subject and that it is unclear whether the BMP-2 protein will be delivered to the targeted site at an amount sufficient to produce therapeutic effects. Amended claims 5-8 require the topical application of the BMP-2 producing MSCs to a specific site on the subject that requires new bone, cartilage or connective tissue formation. Furthermore, the BMP-2 producing MSCs can be reapplied as needed, such that the proper amount of BMP-2 protein is administered to the site. As such, Applicants respectfully submit that the BMP-2 protein will be delivered directly to the targeted site in need of treatment in an amount sufficient to produce therapeutic effects.

In view of the above, Applicants submit that claims 5-8 are properly enabled as required by 35 U.S.C. § 112, first paragraph, and the withdrawal of this rejection is respectfully requested.

III. Rejections under 35 U.S.C. § 102(b)

The Office rejects claims 1-2 under 35 U.S.C. § 102(b) as allegedly anticipated by Moutsatsos et al. (WO 99/11664). This rejection is respectfully traversed for the reasons set forth below.

Claim 1, as amended, is directed to a pharmaceutical composition for topical application at a site requiring new bone, cartilage or connective tissue formation in a subject, comprising a plurality of bone marrow stromal cells (MSCs) comprising a vector comprising a DNA sequence encoding BMP-2 operably linked to a promoter, and a pharmaceutically acceptable polymer. Claim 2 is dependent on claim 1. Moutsatsos et al. does not teach a pharmaceutical composition for topical application at a site requiring new bone, cartilage or connective tissue formation in a subject. As such, Moutsatsos et al. cannot anticipate the subject matter of the claimed invention, and withdrawal of the rejection is respectfully requested.

The Office rejects claims 1-2 and 4-7 as anticipated under 35 U.S.C. § 102(b) in view of Riew et al. (Calcif. Tissue Int. 63:357-360, 1998). Claims 1-2 and 4-7, as amended, are directed to pharmaceutical compositions and methods of enhancing new bone, cartilage or connective tissue formation in a subject requiring topical application of BMP-2 producing MSCs. Riew et al. teaches implantation of bone marrow stem cells transduced with a recombinant adenoviral vector expressing human BMP-2 into the L5/L6 interspace of rabbits. Riew et al. does not teach or suggest pharmaceutical compositions for topical application or methods of enhancing new bone, cartilage or connective tissue formation in a subject requiring topical application of BMP-2 producing MSCs. Thus, Riew et al. does not teach or suggest every limitation of the claimed

invention and cannot be said to anticipate Applicants' invention. Reconsideration and withdrawal of this rejection is respectfully requested.

Claims 1-2 and 4-7 are also rejected under 35 U.S.C. § 102(b) in view of Riew et al. (Calcif. Tissue Int. 68:87-94, 2001). Amended claims 1-2 and 4-7 are directed to pharmaceutical compositions for topical application and methods of enhancing new bone, cartilage or connective tissue formation in a subject requiring topical application of BMP-2 producing MSCs. Cheng et al. teaches implantation of bone marrow stem cells transduced with a recombinant adenoviral vector expressing human BMP-2 into the L5/L6 interspace of rabbits. Cheng et al. does not teach or suggest pharmaceutical compositions for topical application or methods of enhancing new bone, cartilage or connective tissue formation in a subject requiring topical application of BMP-2 producing MSCs. As such, Applicants' claims are not anticipated by Cheng et al., and reconsideration and withdrawal of this rejection is respectfully requested.

IV. Rejections under 35 U.S.C. § 103(a)

Claims 1 and 3-8 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Moutsatsos et al. (Calcif. Tissue Int. 63: 357-360, 1998), in view of Riew et al. (Calcif. Tissue Int. 63: 357-360, 1998) or Cheng et al. (Calcif. Tissue Int. 68:87-94, 2001). The Office also rejected claims 1, 3, 5 and 8 under 35 U.S.C. § 103(a) as being unpatentable over Riew et al. or Cheng et al. These rejections are respectfully traversed for the reasons set forth below.

As discussed above, claims 1 and 3-8 are directed to pharmaceutical compositions for topical application and methods of enhancing new bone, cartilage or connective tissue formation in a subject requiring topical application of BMP-2 producing MSCs. Neither Moutsatsos et al.,

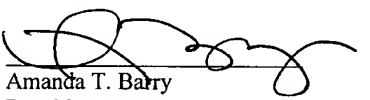
Riew et al., nor Cheng et al. teach or suggest pharmaceutical compositions for topical application or methods of enhancing new bone, cartilage or connective tissue formation in a subject requiring topical application of BMP-2 producing MSCs. The deficiencies of Moutsatsos et al., Riew et al. and Cheng et al. are not cured by the disclosures of the others. As such, Applicants' claims are not made obvious by the disclosures of Moutsatsos et al., Riew et al. or Cheng et al. and withdrawal of the rejections under 35 § 103(a) is respectfully requested.

CONCLUSION

The amendments made herein should in no way be construed as dedicating any unclaimed or amended subject matter or equivalents to the public, and were done solely to expedite prosecution. Applicant reserves the right to pursue any cancelled or amended subject matter in this or related applications.

With entry of the above amendments and in view of the foregoing remarks, it is respectfully submitted that the pending claims are in condition for allowance. The Examiner is encouraged to contact the undersigned with any questions or to otherwise expedite prosecution.

Respectfully Submitted,



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In re Chang
Appln. No. 09/837,217

Version with Markings to Show Changes Made

IN THE CLAIMS:

1. (Amended) A pharmaceutical composition for topical application at a site requiring new bone, cartilage or connective tissue formation in a subject, comprising a plurality of bone marrow stromal cells (MSCs) comprising [an adenovirus mediated human BMP-2 gene] a vector comprising a DNA sequence encoding BMP-2 operably linked to a promoter, and a pharmaceutically acceptable polymer.

4. (Amended) The composition as recited in Claim 1 wherein the polymer is [Pancogene S] collagen type I.

5. (Amended) A method of [treating a bone or other tissue defect] enhancing new bone, cartilage or connective tissue formation in a subject, comprising:

a. obtaining a plurality of bone marrow stromal cells (MSCs) from a subject;

b. [transferring a BMP-2 gene to the MSCs to form] transducing the MSCs of step a) with a vector comprising a DNA sequence encoding BMP-2 operably linked to a promoter to generate BMP-2 protein producing MSCs; and

c. [implanting the] topically applying the BMP-2 protein producing MSCs [to] at a site requiring new bone, cartilage or connective tissue formation on the subject;

such that new bone, cartilage or connective tissue formation is enhanced.

7. (Amended) The method as recited in Claim 5 further comprising mixing the BMP-2 producing MSCs with a polymer either before, during or after [the implantation of] topically applying the protein producing MSCs.

8. (Amended) The method as recited in Claim 5 wherein the protein producing MSCs [implanted] are [present] topically applied in a concentration of about 50×10^6 per ml of a pharmaceutically acceptable polymer and produce an effective amount of the protein.

Pending Claims as of March 6, 2003

IN THE CLAIMS:

1. A pharmaceutical composition for topical application at a site requiring new bone, cartilage or connective tissue formation in a subject, comprising a plurality of bone marrow stromal cells (MSCs) comprising a vector comprising a DNA sequence encoding BMP-2 operably linked to a promoter, and a pharmaceutically acceptable polymer.

2. The composition as recited in Claim 1 wherein the polymer is selected from a group consisting of alginate and collagen.

3. The composition as recited in Claim 1 wherein the MSCs are present in a concentration of about 50×10^6 per ml of the polymer.

4. The composition as recited in Claim 1 wherein the polymer is collagen type I.

5. A method of enhancing new bone, cartilage or connective tissue formation in a subject, comprising:

a. obtaining a plurality of bone marrow stromal cells (MSCs) from a subject;

b. transducing the MSCs of step a) with a vector comprising a DNA sequence encoding BMP-2 operably linked to a promoter to generate BMP-2 protein producing MSCs; and

c. topically applying the BMP-2 protein producing MSCs at a site requiring new bone, cartilage or connective tissue formation on the subject;

such that new bone, cartilage or connective tissue formation is enhanced.

6. The method as recited in Claim 5 wherein the BMP-2 gene is transferred via an adenovirus.

7. The method as recited in Claim 5 further comprising mixing the BMP-2 producing MSCs with a polymer either before, during or after topically applying the protein producing MSCs.

8. The method as recited in Claim 5 wherein the protein producing MSCs are topically applied in a concentration of about 50×10^6 per ml of a pharmaceutically acceptable polymer and produce an effective amount of the protein.